Research article

# Combinative evaluation of primary tumor and lymph nodes in predicting pelvic lymphatic metastasis in early-stage cervical cancer: A multiparametric PET-CT study

Li Kexin, Sun Hongzan*, Guo Qiyong

*Department of Radiology, Shengjing Hospital of China Medical University, Sanhao Street No36, Heping District, Shenyang, Liaoning, 110004, PR China*

A B S T R A C T

*Purpose:* The purpose of this study is to investigate the value of combining tumor and pelvic lymph node (PLN) characteristics on PET-CT in predicting PLN metastasis of patients with early-stage cervical cancer, specifically to further reduce the false-negative cases of diagnosis.

*Methods:* The [18F] FDG PET-CT imaging data of 394 patients who were newly diagnosed with cervical cancer (FIGO stage, Ia-IIa) were retrospectively studied. We measured size, total lesion glycolysis (TLG) of tumor, metabolic tumor volume (MTV), maximum and mean standardized uptake value (SUVmax, SUVmean) of tumor and lymph node (LN). Diagnostic efficiency was evaluated using receiver operator characteristic (ROC) curve. We also investigated additional CT diagnosis information in PET-negative cases.

*Results:* Our results indicated both lymph node and tumor parameters were independent risk factors for lymphatic metastasis in early-stage cervical cancer. The diagnosis based on above meaningful parameters, we name it 'combination diagnosis', offered significantly higher predictive value than that based on SUV measurement alone, which the values of AUC were 0.842 and 0.784 respectively (P < 0.05). In PET-negative cases, we also found that tumor TLG, suspicious LN in lymphatic drainage pathway, long/short axis of LN ≤ 2, heterogeneity of LN significantly associated with PLN metastasis. ROC analysis showed combination diagnosis of all these parameters above produced an AUC value of 0.859 (P < 0.05, 95% CI, 0.811–0.899), which was significantly higher than either using tumor TLG alone (AUC = 0.622, Z = 3.919, P < 0.05) or indices derived from CT alone (AUC = 0.727, 0.668, 0.695. Z = 3.620, 5.356, 3.696, P < 0.05).

*Conclusions:* We proposed a combination diagnosis method that can better predict PLN metastasis for patients with early-stage cervical cancer. In PET-negative cases, combination diagnosis of TLG of tumor and CT indicators also produced improved prediction by reducing false-negative cases of diagnosis. This combination diagnosis approach has significant implications in cervical cancer patient management and treatment planning.

## 1. Introduction

Cancer is one of the public health problems worldwide. The latest data showed that uterine cancer incidence rate increased slightly over the past eight years and cervical cancer is the second leading cause of cancer death in women, especially in the young [1].

Clinical decision making for the treatment of cervical cancer is according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Although FIGO staging is not affected by LN metastasis, it is of importance to diagnose LN metastasis because it has important role in both patient prognosis [2] and postoperative treatment planning [3]. Recent researches demonstrated that lymphatic metastasis rate is usually about 20%– [4–6]. Pelvic lymphadenectomy

is often associated with radical hysterectomy, but excessive excision can cause a series of LN complications such as lymphocysts and lower extremity lymphedema [7].

Pre-treatment imaging examination has become more and more important to evaluate tumor and metastasis in cervical cancer. Amongst various imaging methods, 2-deoxy-2-[18 F]fluoro-D-glucose PET-CT plays an increasingly important role in early diagnosis, treatment planning and prognosis evaluation [8,9]. PET-CT diagnoses tumors by detecting both anatomical and metabolic information [10]. Recently, several studies confirmed certain relationship between the metabolic parameters of [18 F]FDG PET and clinicopathological characteristics of cervical cancer [4,11–13] such as tumor staging, deep cervical stromal invasion, lymph node metastasis, per-therapeutic recurrence and

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* Corresponding author.
 *E-mail address:* sunhongzan@126.com (H. Sun).

prognosis.

Although PET-CT has shown its capability of evaluating preoperative LN metastasis in multiple types of tumor with high accuracy [4], missed diagnosis still exists posing a clinical challenge. This is primarily due to the following reasons. Firstly, the diagnosis based on uniparameter quantification, i.e., SUV measurement, is suboptimal, which may not provide sufficient or comprehensive information for predicting metastasis. Secondly, the limited spatial resolution of PET images may inherently mask small-volume lesions, such as LNs [14]. Thirdly, physiologic bowel motion may adversely affect the detection of small LNs [14]. To the best of our knowledge, existing studies have not investigated the roles of multiparameter PET-CT and tumor characteristics in predicting PLN metastasis in early-stage cervical cancer. Our objective is to demonstrate the value of 'combination diagnosis' (multiparametric PET-CT and tumor characteristics) in predicting PLN metastasis and to reduce missed diagnosis in PET-negative cases.

## 2. Materials and methods

### 2.1. Patients

This retrospective study included 394 patients who were newly diagnosed cervical cancer in the Department of Obstetrics and Gynecology at Shengjing Hospital Affiliated to China Medical University from January 2013 to June 2017. All the patients underwent pretreatment PET-CT scans and FIGO staging before radical hysterectomy. The inclusion criteria were as follows: pathologically proven cervical cancer, FIGO clinical stage was between IA1 and IIA2 stage, absence of distant metastasis or other malignancies, no treatments prior to surgery [15].

### 2.2. PET-CT scan and image acquisition

Before PET-CT scans, all the patients fasted at least 6 h with serum level being lower than 7 mmol/L. Before PET-CT (Discovery PET-CT 690; GE Healthcare, USA) scanning, patients rested quietly for 1 h postinjection of 3.7 MBq/kg [18 F]FDG (produced by MiniTrace II and TracerLab FX-FDG purity > 99%; GE Healthcare, Waukesha, Wisconsin, USA). Then, CT imaging was performed on patients from the top of skull to the mid-thigh (voltage, 120 kV; Auto mA; noise index, 25; slice thickness, 3.27 mm). After that, three-dimensional PET acquisition was immediately conducted (speed, 1.5 min/bed, 7~8 beds in total; matrix size, 192 × 192). The attenuation-corrected PET images were reconstructed using ordered-subsets expectation maximization iterative reconstruction algorithm (24 subsets and 2 iterations), time-of-fight and point-spread-function techniques [15,16].

### 2.3. PET-CT diagnosis and image analysis

Volume computerized-assisted reporting (PET VCAR; GE Healthcare, USA) was used to automatically create volume-of-interest (VOI) by iterative adaptive algorithm on Advantage Workstation (AW) 4.6 (AW 4.6, GE Healthcare, USA), which can generate SUVmax, SUVmean, MTV, TLG. MTV was calculated using the 40% threshold method [17]. Two observers with more than 5-year experience in nuclear medicine and radiology independently evaluated PET-CT and CT images in the blind manner.

### 2.4. Pathological diagnosis

Postoperative pathologic tissue was saved in pathology department of our hospital, processed and embedded in paraffin routinely. 4–6 μm serial sections were cut and stained with haematoxylin-eosin (HE). Two pathologists make the diagnosis in the blind manner. The following information was collected: pathological histology type, pathological differentiation grade, cervical stromal invasion depth, LN metastasis,

**Table 1**
Patient characteristics.

| Characteristic | n (%) |
|---|---|
| Age (median) (years) | 49.00 |
| Age (range) (years) | 28-70 |
| Pathological type | |
| SCC | 344 (87.31) |
| Non-SCC | 50 (12.69) |
| FIGO stage | |
| I | 239 (60.66) |
| II | 155 (39.34) |
| Tumor grade | |
| Well differentiated | 68 (17.26) |
| Moderately differentiated | 281 (71.32) |
| Poorly differentiated | 45 (11.42) |
| Tumor size | |
| ≥ 4 cm | 121 (30.71) |
| < 4 cm | 273 (69.29) |
| Lymphatic metastasis | |
| Yes | 90 (22.84) |
| No | 304 (77.16) |
| Depth of cervical stromal tumor invasion | |
| ≥ 1/2 | 283 (71.83) |
| < 1/2 | 111 (28.17) |

lymphatic vascular space invasion, vagina metastasis, and parametrium metastasis.

### 2.5. Statistical analysis

Cohen's kappa statistic was used to determine the consistency of the results from two observers (0–0.6 as poor consistency, 0.61–0.80 as moderate consistency, and 0.81–1 as high consistency). Univariate and multivariate logistic regression analysis was applied to select variables and construct prediction model. To evaluate the performance of prediction for lymphatic metastasis, all the parameters were examined through ROC curve analysis and Z test, The AUC was calculated. Results were considered statistically significant at the 5% critical level (P < 0.05). All statistical analyses were performed using MedCalc (version 15.2.2, MedCalc Software bvba, Ostend, Belgium) [15].

## 3. Results

### 3.1. Patient information

Clinicopathological characters of patients were summarized in Table1. A total of 394 patients with a median age of 49.00 years were included in this study, age ranging from 28 to 70 years. FIGO stages ranged from Ia to IIa. 90 (90/394) patients had lymphatic metastasis proven pathologically, while 283 (283/394) patients had a cervical stromal invasion depthbeing ≥ 1/2.

### 3.2. Cohen's kappa statistics

Diagnostic consistency between two observers was calculated with the information regarding PET-CT diagnosis, diameter, homogeneity of LN, and LN position. Kappa values were 0.882, 0.981, 0.883, 0.967 (P < 0.05), indicating high consistency rate.

### 3.3. Qualitative analysis results of PET-CT for PLN metastasis and prediction model for PLN metastasis in all cases

Qualitative analysis results of PET-CT to diagnose pelvic LN metastasis showed that AUC was 0.784, sensitivity was 57.8% and specificity was 93.1%.

The results of the logistic regression model for predicting PLN metastasis are shown in Table 2. Univariate analysis revealed that tumor

**Table 2**
Multivariate analysis of both tumor and lymph nodes to predict lymphatic metastasis.

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| Diameter | 6.29 (3.78, 10.46) | 0.000 | | |
| **Tumor size** | | | | |
| ≥ 4 cm | **5.45 (3.22, 9.22)** | **0.000** | **2.27 (1.06, 4.86)** | **0.0344** |
| SUVmaxT | 1.00 (0.97,1.04) | 0.862 | | |
| SUVmeanT | 0.98 (0.921.04) | 0.467 | | |
| **TLG T** | **5.04 (2.61, 9.74)** | **0.000** | **3.303(1.766, 6.179)** | **0.000** |
| MTV T | 4.80 (2.69, 8.54) | 0.000 | | |
| **SUVmaxLN** | **39.38(15.64, 99.15)** | **0.000** | **4.98(1.32, 18.80)** | **0.0178** |
| **SUVmeanLN** | **75.92(17.58, 327.81)** | **0.000** | **11.13 (1.61,76.79)** | **0.0145** |
| MTVLN | 1.086(0.769, 1.533) | 0.639 | | |
| TLGLN | 48.67(16.480,143.77) | 0.000 | | |
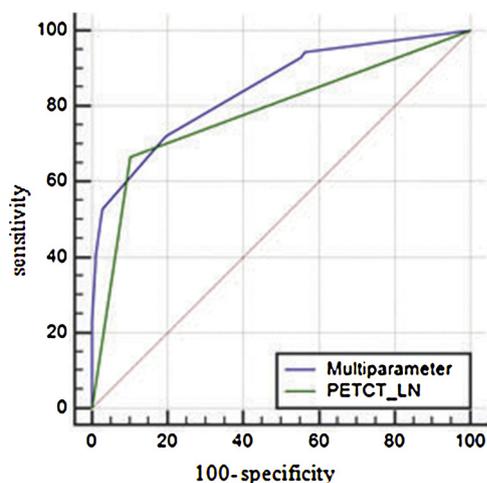


**Fig. 1.** Qualitative analysis results of PET-CT to diagnose pelvic LN metastasis showed that AUC was 0.784 (P < 0.05, 95% CI 0.730–0.831), sensitivity was 57.8% and specificity was 93.1%. AUC of combination tumor size, TLG of tumor, SUVmax with SUVmean of LN is 0.842 (P < 0.05, 95% CI 0.793–0.883), better than qualitative analysis above (Z = 2.272, P < 0.05). Specificity is 80.10%and sensitivity is 71.43%.

size, MTV and TLG of tumor, tumor diameter, SUVmax, SUVmean, TLG of LN significantly associated with PLN metastasis. The final model yielded four statistically significant predictors: tumor size, TLG of tumor, SUVmax, SUVmean of LN. A prediction model was constructed based on this logistic regression model (Hosmer-Lemeshow test P-value > 0.05). Combination ROC of above parameters and qualitative analysis of PET-CT present with Fig. 1. ROC analysis showed the AUC of combination tumor size, TLG of tumor, SUVmax with SUVmean of LN is 0.842 (P < 0.05, 95%CI 0.793 - 0.883), better than qualitative analysis above (Z = 2.272, P < 0.05). Specificity is 80.10%and sensitivity is 71.43%.

### 3.4. Predicting value of PET-CT in PET-negative cases

The subtype results of the logistic regression model in PET-negative cases for predicting PLN metastasis are shown in Table 3. Multivariate analysis revealed that suspicious LN in lymphatic drainage pathway, long/short axis of LN ≤ 2, heterogeneity of LN and TLG of tumor significantly associated with PLN metastasis. Combination ROC of above parameters presents with Fig. 2. ROC analysis showed the AUC of combination prediction is 0.859 (P < 0.05, 95% CI 0.811 - 0.899). Accuracy is 88.15%, specificity is 92.58% and sensitivity is 68.75%. The combination prediction was better than either TLG of tumor (AUC = 0.622, Z = 3.919, P < 0.05) or index derived from CT alone.

(AUC = 0.727, 0.668, 0.695. Z = 3.620, 5.356, 3.696, P < 0.05).

## 4. Discussion

. The diagnosis of LN metastasis plays a critical role in both patient prognosis and treatment planning. The false-negative rate of diagnosis in PET-negative cases is always a clinical challenge. In this study, we proposed to utilize 'combination diagnosis' to predict pelvic lymph node metastasis in early-stage cervical cancer. We have demonstrated that 'combination diagnosis' (tumor size, TLG, SUVmean, and SUVmax) were significantly superior to SUV diagnosis alone. The combination diagnosis of tumor TLG, and the CT indicators (suspicious LN in lymphatic drainage pathway, long/short axis of LN ≤ 2, heterogeneity of LN) further improves prediction of metastasis in the PET- negative cases.

The independent risk factors of LN metastasis of early cervical cancer were investigated in this study. The results showed that parameters of lymph nodes (SUVmax, SUVmean) and characterization of primary tumors (tumor size and TLG) were all independent risk factors for LN metastasis. In previous studies, SUVmax of LN was normally used to differentiate benign and malignant LNs [18]. It has been proved that the overexpression of glucose transporter-1 in primary tumor will lead to the increase of FDG uptake, which is also associated with LN metastasis in various tumors [19–21]..There are also other studies on the relationship between PET-CT parameters and LN metastasis. For instance, Crivellaro et al [22] demonstrated that tumor MTV and TLG had values in predicting LN metastasis. Another study by Mustafa, et al illustrated that the higher SUVmax tend to indicate LN metastasis in cervical cancer [23]. Husby, et al [24] showed that SUVmean, MTV and TLG can predict LN metastasis in endometrial carcinoma. A similar conclusion was also found in the study of thyroid cancer but the predictive value of MTV, TLG was higher than that of other indicators [25]. We believe that these different findings may attribute to the differences in pathological types, which may lead to varied tumor metabolism. It may also be related to the difference in sample size.

Given the limited sensitivity of PET-CT in diagnosing LNs [26], this study further explored the value of' combination diagnosis' in predicting PLN metastasis in PET-negative cases. We collected and analyzed all available clinicopathological parameters: FIGO staging, depth of tumor invasion, pathological type, differentiation, tumor size, TLG value of primary tumor, LNs in internal iliac artery and obturator region, long/short diameter ratio and internal density. The results showed that the tumor TLG was significantly increased and the round-shape, heterogeneous LNs appeared in the obturator region or the internal iliac artery, the metastasis might be highly suspected, which improved the sensitivity of PET-CT diagnosis to some extent. The results of this study are consistent with recent studies on the lymphatic drainage pathway of cervical cancer [27,28]. The LN metastasis of cervical cancer is mainly through the lateral chain and the lower abdominal chain, and the obturator LN is the sentinel LN in the lateral lymphatic metastasis of cervical cancer. In the lower abdominal metastasis pathway, tumor cells can metastasize along the internal iliac vessels and visceral branches to the LNs of the internal and external iliac junctions [29]. Therefore, the size, location, density of LN and metabolic parameters of primary tumor should be considered in the diagnosis of lymphatic metastasis. Nogami, et al [30] indicate that the efficacy of PET-CT for detecting LN metastasis was limited depending on lesion size and region. The addition of metabolic value of primary tumor can effectively improve the sensitivity of diagnosis in our study. Song et al [31] used a similar method to predict LN metastasis of breast cancer. The results showed that the predictive efficiency was higher than that of single parameter diagnosis. Nakamura, et al [32] included the measurement of SUVmax, LN status and serum squamous cell carcinoma antigen (SCC-Ag) level before treatment showing improved prognosis in cervical squamous cell carcinoma.

However, there were several limitations in our study. Firstly, this is

**Table 3**
Multivariate analysis of metabolic parameters and CT indicators in PET-negative cases.

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | p-value | OR (95% CI) | p-value |
| FIGO staging | 1.436(0.705, 2.926) | 0.319 | | |
| Invasion depth ≥1/2 VS < 1/2 | 2.526(1.020, 6.259) | 0.045 | | |
| Pathologic type Squamous VS non-squamous | 1.603(0.803, 3.201) | 0.181 | | |
| Differentiation | 1.009(0.442, 2.304) | 0.983 | | |
| SCC Ag normal VS abnormal | 1.377(0.678, 2.798) | 0.376 | | |
| Tumor size ≥4 VS < 4 | 3.500 (1.629, 7.522) | 0.001 | | |
| **TLG of tumor** | **2.599(1.159,5.830)** | **0.020** | **0.990 (0.982, 0.998)** | **0.010** |
| **Suspicious LN** | **7.745(3.416,17.560)** | **0.000** | **8.230(2.650, 25.553)** | **0.000** |
| **Long /short axis ≤2VS > 2** | **7.411(2.800,19.614)** | **0.000** | **13.886(3.402, 56.685)** | **0.000** |
| **Heterogeneity or homogeneity** | **7.526(3.492,16.219)** | **0.000** | **11.556(3.986, 33.498)** | **0.000** |
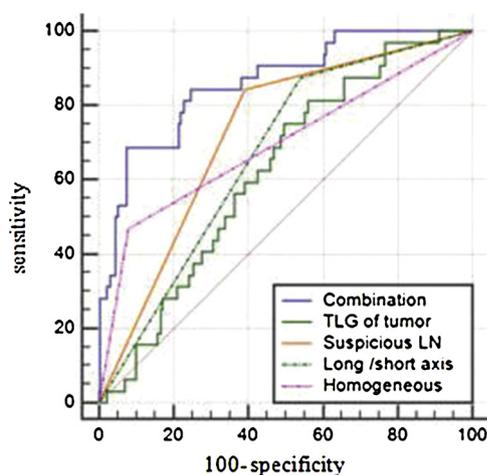


**Fig. 2.** ROC analysis showed the AUC of combination prediction is 0.859 (P < 0.05, 95%CI 0.811 - 0.899). Accuracy is 88.15%, specificity is 92.58% and sensitivity is 68.75%. The combination prediction was better than either TLG of tumor (AUC = 0.622, Z = 3.919, P < 0.05) or index derived from CT alone. (AUC = 0.727, 0.668, 0.695. Z = 3.620, 5.356, 3.696, P < 0.05).

a retrospective study design performed at a single institute. Secondly, as multiple types of carcinoma were enrolled in our study, subgroup analysis in different pathological types will be researched in the future. Finally, our study only focuses on diagnosis, and prognosis evaluation will be thoroughly performed for future study.

## 5. Conclusions

By combining multiparametric PET-CT and tumor characteristics, the combination diagnosis significantly improved the prediction of metastasis for the early-stage cervical cancer patients. The additional information provided on CT images including LN occurring in lymphatic drainage pathway with long/short axis of LN ≤ 2 and heterogeneity of LN can help reduce the missed diagnosis cases in PET-negative cases. This combination diagnosis method can be beneficial for cervical cancer patient management and treatment planning.

## Conflict of interest

The authors declare that they have no conflicts of interest.

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